AF

IMAGE

ATTORNEY DOCKET NO. 13172.0001U1
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	
DEAN et al.	Examiner: Sisson, Bradley L.
Application No. 09/514,113	Art Unit: 1634
Filed: February 28, 2000	Confirmation No.: 9257
For: METHOD FOR REDUCING ARTIFACTS IN NUCLEIC ACID AMPLIFICATION	

TRANSMITTAL OF SUPPLEMENTAL APPEAL BRIEF

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEEDLE & ROSENBERG, P.C.
Customer Number 23859

Dear Sir:

In response to the Office Action rejecting claims 1-19, 21-23, 27, 31-45 and 77-80, mailed July 13, 2004 and the Advisory Action mailed February 16, 2005 maintaining the rejection of claims 1-19, 21, 22 and 77-80 and pursuant to 37 C.F.R. § 41.37 and former 37 C.F.R. § 1.193(b)(2), enclosed is a Supplemental Appeal Brief.

It is believed that no additional fee is required with this submission. 35 U.S.C. § 134 states that "an applicant for a patent...may appeal from a decision of the primary examiner to the Board of Patent Appeals and Interferences, having *once* paid the fee for such appeal" (emphasis added). The fee for filing an Appeal Brief specified in 37 C.F.R. 41.20(b)(2) was previously paid with the Appeal Brief mailed February 17, 2004. Since applicants have once paid the fee for an appeal in this application, it is believed that no fee for filing of this Supplemental Appeal Brief is

required. However, the Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8

I hereby certify that this correspondence, including any items indicated as attached or included, is being deposited with the United States Postal Service as First Class Mail, in an envelope addressed to: Mail Stop Appeal Brief-Patents, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on the date indicated below.

Robert A. Hodges — Date: 9/6/2005

ATTORNEY DOCKET NO. 13172.0001U1
PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appellants	:	Dean *et al.*	Group Art Unit: 1634
Application No.	:	09/514,113	Examiner: Bradley L. Sisson
Filed	:	February 28, 2000	Confirmation No. 9257
For	:	METHOD FOR REDUCING ARTIFACTS IN NUCLEIC ACID AMPLIFICATION	

SUPPLEMENTAL APPEAL BRIEF UNDER 37 CFR § 41.37

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

NEEDLE & ROSENBERG, P.C.
Customer Number 23859

Sir:

This is an appeal pursuant to 35 U.S.C. § 134 from the Examiner's decision rejecting claims 1-19, 21-23, 27, 31-45 and 77-80, mailed July 13, 2004 and the Advisory Action mailed February 16, 2005 maintaining the rejection of claims 1-19, 21, 22 and 77-80.

I. Real party in interest

The real party in interest of this application is QIAGEN GmbH, assignee of the inventor's entire interest.

II. Related appeals and interferences.

None.

III. Status of claims.

Claims 1-19, 21, 22 and 50-80 are pending. Claims 20 and 23-49 have been cancelled. Claims 50-76 have been withdrawn from consideration as directed to a non-elected invention,

pursuant to the restriction requirement made in the Office Action dated October 25, 2000, and Appellants' election made in the communication dated January 9, 2001. The status of the claims reflects the Amendment mailed on December 13, 2005, which Amendment was entered by the Examiner in the Advisory Action mailed February 16, 2005. Claims 1-19, 21, 22 and 77-80 stand rejected and claims 1-19, 21, 22 and 77-80 are subject of this appeal. The text of the claims on appeal are set forth in the Appendix 1 to this Supplemental Appeal Brief.

IV. Status of amendments.

An Amendment canceling claims 23, 27 and 31-45 was mailed on December 13, 2005 and was entered by the Examiner in the Advisory Action mailed February 16, 2005..

V. Summary of claimed subject matter.

The claims on appeal are drawn to a method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer (page 5, line 11, through page 6, line 21; page 19, line 6 through page 20, line 21; and Figures 1, 2, 3 and 5). The method of claims 1-19, 21-22 and 77-80 require that the template-deficient oligonucleotide comprises one or more template-deficient nucleotides (page 5, line 21 through page 6, line 21), wherein the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction (page 5, line 21, through page 6, line 8; page 12, line 29, through page 13, line 17; and page 18, lines 22-29).

Claim 77 requires that the one or more adjacent template-deficient nucleotides are within three nucleotides of the 5' end of the template-deficient oligonucleotide (page 6, lines 18-20). Claim 79 requires that the modified nucleotides are abasic (page 6, lines 25-26; page 7, line 9; page 8, lines 22-26; page 11, line 22-23; page 12, lines 22-23; page 16, lines 10-11; Examples 1 and 2; and Figures 2, 3, 6, and 7). Claim 80 requires that the one or more adjacent template-deficient nucleotides are within three nucleotides of the 5' end of the template-deficient oligonucleotide and that the modified nucleotides are abasic (Example 1, specifically at page 21, lines 12-23).

VI. Grounds of rejection to be reviewed on appeal.

The grounds of rejection for review are:

(1) the rejection of claims 1-19, 21, 22 and 77-80 under 35 U.S.C. § 112, second paragraph, as being indefinite;

(2) the rejection of claims 1-19, 21, 22 and 77-80 under 35 U.S.C. §101 as an improper process claim;

(3) the rejection of claims 1, 5, 8-10, 19, 22 and 77 under 35 U.S.C. § 102(a) and (e) as being anticipated by Wallace (U.S. Patent No. 6,027,923);

(4) the rejection of claims 1-19, 21, 22 and 77-80 under 35 U.S.C. § 102(e) and 35 U.S.C. § 103(a) as being anticipated by, or in the alternative, obvious over Van Ness *et al.* (U.S. Patent No. 6,361,940 B1); and

(5) the rejection of claims 1-19, 21, 22 and 77-80 under 35 U.S.C. § 103(a) as being unpatentable over Van Ness *et al.* (U.S. Patent No. 6,361,940 B1) in view of Gildea *et al.* (U.S. Patent No. 6,265,559 B1) or Egholm *et al.* (U.S. Patent No. 6,316,230 B1).

VII. Argument.

A. Rejection Under 35 U.S.C. § 112, second paragraph

Claims 1-19, 21, 22 and 77-80 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Appellants regard as the invention. Appellants respectfully traverse this rejection.

1. The issues

Claims 1-19, 21, 22 and 77-80 are alleged to be indefinite on the basis that because the claims allegedly do not provide any step involved in the claimed process, it is allegedly unclear what method/process the claims are intended to encompass. Thus, the issues are (1) do the claims recite a process step and (2) are the metes and bounds of the claims reasonably definite. Although it is not clear from the rejection set forth in the Office Action mailed July 13, 2004 whether the claims are considered to be improper "use" claims, are alleged to be indefinite as to what the claims encompass, or both, Appellants assert that the claims are not improper use claims and that it is clear what the claims encompass. Appellants provide arguments on both issues below.

Appellants assert that (1) present claims all include a positive process step: "conducting a nucleic acid amplification reaction" (which is recited in each of the independent claims 1, 77, 79 and 80), and thus are not an improper "use" claims; (2) the claims, although defining the use of the claimed template-deficient oligonucleotides broadly, adequately define the metes and bounds of the claimed method, and (3) those of skill in the art would understand the metes and bounds of the claimed method.

2. The legal standard

35 U.S.C. § 112, second paragraph requires that: "The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which applicant regards as his invention." 35 U.S.C. § 112. Thus, Appellants are allowed to claim what they consider to be their invention. To comply with the requirements of 35 U.S.C. § 112, second paragraph, a claim need only be understandable to those of skill in the relevant art and need only be reasonably definite. *In re Hayes Microcomputer Products Inc Patent Litigation*, 982 F.2d 1527, 1534-35, 25 U.S.P.Q.2d 1241, 1246 (Fed. Cir. 1992); *In re Moore*, 439 F.2d 1232, 1235, 169 U.S.P.Q. 236, 238 (CCPA 1971). A claim is to be understood in light of the specification. *See Morton Int'l, Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1470, 28 U.S.P.Q.2d 1190, 1195 (Fed. Cir. 1993). Breadth in a claim does not make a claim indefinite. *In re Miller*, 441 F.2d 689, 693, 169 U.S.P.Q. 597, 600 (CCPA 1971).

3. The claims include a positive process step

Independent claims 1, 77, 79 and 80 all recite a positive process step: "conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer." The rejection makes the error of focusing on the "use" of the template-deficient primer in the nucleic acid amplification reaction while ignoring the fact that the claims require that an amplification reaction be conducted. Although use of the template-deficient oligonucleotides can be, by itself, a proper method step (as discussed below), the present claims include another clear and acceptable method step. Thus, even if the recited "use" of the template-deficient oligonucleotide did not constitute a proper method step, the claims would meet the requirements of 35 U.S.C. § 112, second paragraph, at least because of the method step "conducting a nucleic acid

amplification reaction." For these reasons, the claims meet the requirements of 35 U.S.C. § 112, second paragraph.

4. **Use of oligonucleotides as primers in an amplification reaction is a sufficient process step**

The present rejection appears to be (improperly) based on a per se rule that recitation of "use" in the claims renders the claims indefinite under 35 U.S.C. § 112, second paragraph. For example, the rejection provides no rationale or explanation for why or how the present claims fail to reasonably set forth the metes and bounds of the claimed method. Rather, the rejection merely states that "[a] claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced". This legal principle is, however, limited to claims that completely lack any positive process step (see discussion below in connection with rejection under 35 U.S.C. § 101). Claims that include even one minimal positive process step are definite and should not be rejected as improper "use" claims. *Ex parte Porter*, 25 U.S.P.Q.2d 1144, 1147 (BPAI 1992); see also MPEP 2173.05(q). Regarding the legal premise underlying the present rejection (that recitation of a "use" of something is an improper method step), Appellants note that *Ex parte Porter* found the single step of "utilizing" in a claim to be definite and to be statutory subject matter. *Porter* at 1147. Claim 6 of the Porter application ("A method for unloading nonpacked, nonbridging and packed, bridging flowable particle catalyst and bead material from the opened end of a reactor tube which comprises utilizing the nozzle of claim 7") clearly recited the step of "utilizing" but was held in *Porter* to be not indefinite under 35 U.S.C. 112, second paragraph. *Porter* at 1147. The Board in *Porter* states that "...we do not agree with the examiner that the claim is either ambiguous or non-

statutory." *Id.* The Board in *Porter* also stated "[t]he manner in which claim 6 has been drafted has been an acceptable format for years. . . Contrary to the examiner's assertion that claim 6 has no method step, the claim clearly recites the step of 'utilizing.' Such single – step method claims were present in *In re Kuehl* . . ." *Id.* The claim in *Kuehl* cited with approval in *Porter* reads "A hydrocarbon conversion process which comprises contacting a hydrocarbon charge under catalytic cracking conditions with the composition of claim 6." *In re Kuehl*, 475 F.2d 658, 659, 177 U.S.P.Q. 250, 251 (CCPA 1973). Thus, it is clear that a single broad step, even a step that amounts to a "use," can be proper and statutory.

Applying this standard to the present claims, it is clear that "using a template-deficient oligonucleotide as a primer" in an amplification reaction constitutes a sufficient process step to render the claims proper method claims even if the "conducting a nucleic acid amplification reaction" step was not also present in the claims. For these additional reasons, the claims meet the requirements of 35 U.S.C. § 112, second paragraph.

5. The metes and bounds of the claims are sufficiently definite

The claims on appeal involve "a method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer..." Thus, the claims involve conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer. The specification refers to some nucleic acid amplification methods on page 1, lines 7-21, and defines and describes nucleic acid amplification reactions at least from page 9, line 3, to page 10, line 5. Such nucleic acid amplification reactions make use of oligonucleotide primers and those of skill in the art are well aware of this. Although such reactions are broadly covered,

this does not make the scope of the claims indefinite. *Miller*, 441 F.2d at 693, 169 USPQ at 600. The specification also provides extensive description for the claimed template-deficient oligonucleotides (see, for example, from page 11, line 7, to page 12, line 3, and from page 5, line 21, to page 9, line 2).

Thus, it is not seen how or why those of skill in the art could misinterpret the claims or be unsure of their scope. The rejection does not provide any explanation for why or how those of skill in the art would fail to understand the claims. If it is a nucleic acid amplification reaction where the specified primer is used in any way, it is covered by the claims. Appellants submit that those of skill in the art know what constitutes a nucleic acid amplification reaction (especially in light of the specification) and would surely know when the claimed primers are being used in such a nucleic acid amplification reaction. Armed with the Appellants' disclosure and claims along with the teachings of the prior art concerning the numerous nucleic acid amplification techniques using primers, one of skill in the art would certainly be able to interpret the metes and bounds of the claim. For these additional reasons, the claims meet the requirements of 35 U.S.C. § 112, second paragraph.

6. **The rejection fails to establish that those of skill in the art would not understand the use of the template-deficient oligonucleotides as claimed**

The entire rationale of the present rejection, as set forth in the Office Action mailed July 13, 2004 (pages 3-4), reads:

> Claims 1, 21, 22, 77, 79, and 80 provides for the use of template deficient oligonucleotides, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to

encompass. A claim is indefinite where it merely recites a use without any active, positive steps determining how this use is practiced.

The rejection fails to establish that those of skill in the art would not understand the use of the template-deficient oligonucleotides as claimed and fails to provide any rationale for why the claims are not reasonably clear, which is all the law requires. The rejection merely asserts without support that some unspecified additional detail must be recited in the claims but does not establish why or how the law requires it. Because the rejection fails to meet this burden, the rejection fails to establish a *prima facie* case of indefiniteness. At least for this reason, the present rejection should be reversed.

B. Rejection Under 35 U.S.C. § 101

Claims 1-19, 21, 22 and 77-80 stand rejected under 35 U.S.C. § 101 on the basis that the claims are not proper process claims. Appellants respectfully traverse this rejection.

The rejection alleges that "the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101." Office Action mailed July 13, 2004, page 4. Thus, the present rejection is based on the unpatentability of claims drawn solely to the "use" of a material without reciting any steps in the process. Appellants first note that the rejection fails because the claims do recite a process step. As discussed above, independent claims 1, 77, 79 and 80 all recite a positive process step: "conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer." This step makes the claims statutory. Reference in the claims to "using a template-deficient oligonucleotide as a primer" does not convert a statutory claim into a non-statutory claim and the rejection cites no authority

or rationale by which this would be the case. The rejection fails to make out a proper *prima facie* case for lack of statutory subject matter at least by failing to identify how a claim that recites a positive process step could constitute non-statutory subject matter. Further, it is clear that "using a template-deficient oligonucleotide as a primer" in an amplification reaction (as recited in the claims) constitutes a sufficient process step to render the claims proper method claims even if the "conducting a nucleic acid amplification reaction" step was not also present in the claims. For these reasons, the claims meet the requirements of 35 U.S.C. § 101.

The rejection cites the decisions in *Ex Parte Dunki*, 153 U.S.P.Q. 678 (BPAI 1967), and *Clinical Products Ltd. v. Brenner*, 255 F. Supp. 131, 149 U.S.P.Q. 475 (D.D.C. 1966). These cases are distinguishable from the present claims. *Dunki* and *Clinical Products* stand for the proposition that recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. The claims at issue in *Dunki* and *Clinical Products* completely lacked any positive process claim. It was this total lack of any process claim that led the Board in *Dunki* and the court in *Clinical Products* to hold the claims at issue there unpatentable. Specifically, the court in *Clinical Products* held that the word "use" alone in the claims at issue there did not describe a process, and therefore the form of the claims at issue did not come within any of the statutory classes of patentable subject matter set forth in 35 U.S.C. § 101. *Clinical Products,* 255 F. Supp. at 135, 149 U.S.P.Q. at 426. In contrast, if a claim has any minimal process step, it is statutory subject matter. Because the present claims include a positive process step ("conducting a nucleic acid amplification reaction") the claims do define a process and are therefore statutory subject matter under 35 U.S.C. § 101.

For the reasons set forth above, Appellants assert that the claims constitute statutory subject matter. Therefore, Appellants respectfully request reversal of this rejection.

C. Rejections of claims 1, 5, 8-10, 19, 22 and 77 under 35 U.S.C. § 102(a), (e) as anticipated by Wallace

1. Arguments for claims 1, 5, 8-10, 19, 22 and 77

Claims 1, 5, 8-10, 19, 22 and 77 are patentable over Wallace for several reasons. First, Wallace fails to disclose any oligonucleotide used in a nucleic acid amplification reaction where the number and composition of template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3'end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction. Second, it is actually a major goal of Wallace to prevent the primers from effectively priming nucleic acid synthesis in the nucleic acid amplification reaction of Wallace. Third, Wallace fails to disclose use of the primers in any nucleic acid amplification reaction where the 3' end nucleotides alone can effectively prime nucleic acid synthesis.

i. The issues

Appellants submit that the present rejection depends on the proper understanding of what the prior art discloses, the proper understanding of what the current claims require, the proper understanding of the law of the novelty requirement as it applies to the claimed method, and a proper application of that law to the claimed method. Appellants note that the rejection has failed to achieve any of these goals.

The rejection contends that Wallace teaches all of the limitations of the claimed invention. The rejection focuses and relies on an erroneous assumption that a particular sub-

region of the Wallace primers is sufficient to allow the nucleotides in this sub-region to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction.

ii. The legal standard

Anticipation requires strict identity: each and every element of the claimed invention must be identically set forth in a single prior art reference. *See PIN/NIP, Inc. v. Platte Chemical Co.*, 304 F.3d 1235 (Fed. Cir. 2002).

iii. The claims on appeal

The present claims are drawn to a method useful for reducing the formation of artifacts during nucleic acid amplification reactions that involves conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer. Use of the template-deficient oligonucleotides reduces the chance that the oligonucleotide could serve as an effective template in the formation of artifacts. The claims recite specific structures and properties for the template-deficient oligonucleotides. Specifically, independent claims 1 and 77 (from which the remaining claims under rejection depend) provides "...wherein the number and composition of template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3'end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction" (emphasis added). A careful reading of this claim language shows that the claims identify:

(A) a particular nucleotide in the oligonucleotide (hereinafter "nucleotide (A)", defined as "the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide"),

(B) a particular sub-region of the oligonucleotide (hereinafter "sub-region (B)", defined as the "nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide"--that is, nucleotides 3' of nucleotide (A)), and

(C) a property of this particular sub-region (hereinafter "property (C)", wherein "the number and composition of template-capable nucleotides [in sub-region (B)] is sufficient to allow the template-capable nucleotides [in sub-region (B)] alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction").

Note that property (C) is a property of sub-region (B) alone, not of the template-deficient oligonucleotide as a whole. This distinction is crucial. Further, the claim language also makes clear that property (C) is in reference to the capability of sub-region (B) "in the nucleic acid amplification reaction" (emphasis added). That is, property (C) is not a universal property of the oligonucleotide, exhibited in any and all nucleic acid amplification reactions, but rather is a property that need be present only in the particular nucleic acid amplification reaction being performed. A given oligonucleotide may meet this limitation (i.e., property (C)) in some nucleic acid amplification reactions and not others.

Appendix 3 is a diagram of an example of a template-deficient oligonucleotide as claimed where nucleotide (A) is highlighted in pink and sub-region (B) is highlighted in green.

iv. Wallace

Wallace discloses a process of amplifying a nucleic acid sequence of interest using "a unique primer, or set of primers...for each nucleic acid strand in the starting sample that contains the sequence to be amplified. The linear accumulation of primer extension products from cycle to cycle is assured through the use of primers that contain non-replicable elements – elements

that halt the primer extension reaction, preventing the nucleic acid polymerase from replicating the entire sequence of the primer." Column 4, line 62, through column 5, line 2 (emphasis added). The method of Wallace involves the use of a primer with a template-deficient nucleotide, but this primer does not have the properties required of the claimed template-deficient oligonucleotides. Appendix 2 is a copy of Wallace Figures 1-4 where the nucleotide analogous to nucleotide (A) as described above is highlighted in pink and the sub-region analogous to sub-region (B) as described above is highlighted in green. As will be seen, Wallace's analog of sub-region (B) lacks property (C) as required by the present claims. Because Wallace fails to disclose each and every feature of the present claims, Wallace fails to anticipate the present claims.

Figures 1 through 4 of Wallace (see Appendix 2) show seven stages (steps (a) through (g)) of the replication of a target sequence using the method and primers disclosed by Wallace. In these figures, the original strands of the target sequence are depicted as solid lines, the primers are depicted by dashed lines, and replicated strands are depicted by dotted lines. Non-replicable nucleotides (i.e. template-deficient nucleotides) are depicted as an "x" or an "o." In Figures 1-4, the template-deficient nucleotides appear in the middle of the primers (see Figure 1, step (b), showing the primers hybridized to the two strands of the target sequence). As the primers are extended, the template-deficient nucleotides are incorporated into the replicated strands (see Figure 1, step (c) (dashed/dotted strands)). Because the primers are incorporated into the strands, the first replicated strands are "full length" (that is, they include all of the primer sequences and primer complement sequences). As a result, the primers are fully complementary to the first replicated strands as depicted in Figure 1, step (d), where primers are shown hybridized to the

two original target sequence strands (top and bottom) and the two first replicated strands (middle two strands).

When the hybridized primers of Wallace are extended on these four strands, the results differ for the original target sequence strands and the first replicated strands. As in the first round of replication, the original target sequence strands are fully replicated (see top and bottom double-stranded products in Figure 2, step (e)). However, the first replicated strands are only partially replicated (see middle two (partially) double-stranded products in Figure 2, step (e)). The partially replicated strands are marked with reference numbers 10 and 20. As can be seen, replication terminated at the template-deficient nucleotides incorporated into the first replicated strands. Thus, two of the second replicated strands (reference numbers 10 and 20) are not full length and their ends do not have a full complement of the primer sequences.

Figure 3, step (f), depicts primer hybridization (and the lack of primer hybridization) to the eight strands from Figure 2, step (e). As can be seen, the primers hybridize to, from top to bottom, the first two strands, the fourth strand, and the last three strands. The primers do not hybridize to the third and fifth strands (and replication of those strands is, as a consequence, not primed by the primers; see Figure 4, step (g)). The third and the fifth strands are the two second replicated strands that are not full length (reference numbers 10 and 20 in Figure 2). The primers do not hybridize because these strands have insufficient sequences complementary to the primers. The strands do have some sequence complementary to the primers. Specifically (and relevantly), they have only sequence complementary to those nucleotides in the primers that are 3' of the template-deficient nucleotide. Thus, as depicted in Figure 3 of Wallace, the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the

3' end of the primers used in Wallace is not sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction of Wallace.

Note that the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the primers of Wallace are the only nucleotides in the primer that are complementary to the second replicated strands that are not full length (reference numbers 10 and 20 in Figure 2). It is also very important to point out that a main goal of Wallace in the use of primers having template-deficient nucleotides is to prevent priming of second generation and later replicated strands by the original primers (see column 2, lines 49 - 53, where Wallace states that "...the second generation primer extension products contain at least a portion of the nucleic acid sequence of interest and cannot serve as templates for the synthesis of extension products of the primers which were extended to synthesize their templates." (emphasis added)).

v. Wallace's primers do not have the properties of Appellants' claims

To anticipate the present claims, Wallace must disclose every element of the claimed method. Appellants submit that Wallace does not disclose any oligonucleotide used in a nucleic acid amplification reaction where the number and composition of template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3'end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction. In other words, and as shown above, Wallace fails to disclose use of any primer that has a sub-region meeting the description of sub-region (B) having property (C) as claimed.

The nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide in the primers of Wallace (the green regions in Appendix 2) are not alone capable of effectively priming nucleic acid synthesis in the nucleic acid amplification reaction of Wallace. That is, the analogous sub-region of the primers of Wallace lacks property (C). The fact that the 3' end regions of the Wallace primers lack property (C) is clearly established in Wallace. That is, the nucleotides 3' of the template deficient nucleotide are not sufficient to prime nucleic acid synthesis (see discussion of Wallace Figures 1-4 (Appendix 2) above). This is exactly the opposite of what the present claims require. Such a deficiency in Wallace is clearly established because if the nucleotides were sufficient to prime nucleic acid synthesis, then the primers of Wallace would produce third and higher generation primer extension (which the primers do not). See, for example, Figures 3 and 4 of Wallace showing that second generation strands (labeled 10 and 20) are not replicated because the primers cannot effectively prime replication. This is because the small portion on the second generation strands that is complementary to the primers is too short (and/or of such composition) for the primers to be able to prime replication effectively (see, for example, Wallace, col. 2, lines 49-53). This small portion corresponds to the nucleotides in the Wallace primers 3' of the template-deficient nucleotide closest to the 3' end of the Wallace primers (which makes it analogous to sub-region (B) of the claimed oligonucleotides). For this reason, the method and primers of Wallace clearly indicate that the primers of Wallace specifically lack a feature recited in the present claims.

Furthermore, preventing these higher generation of primer extension products is a major goal of Wallace. Wallace, column 9, lines 18-25, states "[t]he use of primer that contain non-replicable and/or cleavable elements ensures that, except for primer extension products

synthesized on an original template nucleic acid strand present in the starting material . . .none of the synthetic nucleic acids produced during the process will serve as templates in subsequent rounds of primer extension." This is considered an advantage of the Wallace process as it is stated that "[s]till further advantages are presented as the products accumulate linearly and thus can be accurately quantified; the occurrence of "false positives" will be reduced in comparison with exponential processes that use newly-synthesized DNA as a template in subsequent rounds using the same primer." Wallace, column 13, line 6-11. Again, this is exactly the opposite of the goal of the claimed method where priming by the analogous region of the claimed template-deficient oligonucleotides is required. Because Wallace does not disclose every feature of the claimed method, Wallace cannot anticipate the claimed method.

For the reasons above, Wallace fails to anticipate claims 1, 5, 8-10, 19, 22 and 77. At least for this reason, the present rejection should be reversed.

vi. The allegation that the (B) region of the template-deficient primer of Wallace is considered to exhibit or retain property (C) is misguided

The Advisory Action mailed on October 31, 2003 alleges that there is no evidence of record that would refute the capability of sub-section (B) of the primers of Wallace from exhibiting property (C). The Advisory Action specifically alleges that the sub-region (B) of the primer of Wallace is considered to exhibit or retain property (C). In support, the Advisory Action cites Sommer and Tautz (Nucleic Acids Research 17(16): 6749 (1989); "Sommer") which shows that efficient priming can take place with two 3' nucleotides annealing to the template where a mismatch occurs immediately upstream and notes that the primers of Wallace have three complimentary nucleotides at the 3' terminus of the primer.

Although Sommer does suggest that successful priming can take place with three 3' nucleotides annealing to the template where a mismatch occurs immediately upstream, the primers of Sommer have complementary nucleotides other than those at the 3' end that contribute to hybrid stability of the primers (see Table I in Sommer). The present claims explicitly require that only the nucleotides 3' of the template-deficient nucleotide closest to the 3' end be considered. The present claims require that these nucleotides alone must effectively prime. Sommer does not suggest that this is possible for primers having only two or three complementary nucleotides.

Furthermore, Wallace intentionally and specifically engineered around effective priming by the 3' end nucleotides of the primer. As discussed above a main goal of Wallace in the use of primers having template-deficient nucleotides is to prevent priming of second generation and later replicated strands by the original primers (see column 2, lines 49 - 53, where Wallace states that "...the second generation primer extension products contain at least a portion of the nucleic acid sequence of interest and cannot serve as templates for the synthesis of extension products of the primers which were extended to synthesize their templates." (emphasis added)). Such an effect is considered an advantage of the Wallace process. Wallace, column 13, line 6-11.

The present claims require that the 3' end nucleotides alone be capable of effectively priming nucleic acid synthesis "in the nucleic acid amplification reaction" (emphasis added). Thus, the claims limit the recited priming capability to the nucleic acid amplification reaction involved, not just any nucleic acid amplification. It is unquestionable that the primers of Wallace do not have the priming capability required by the present claims at least because

Wallace explicitly disclaims such a capability in the nucleic acid amplification reactions disclosed in Wallace (the only nucleic acid amplification reactions taught by Wallace).

Wallace only discloses a use of primers in the specific nucleic acid amplification reaction described in Wallace (which reaction is designed to prevent efficient priming from taking place with however many complimentary nucleotides there are at the 3' terminus of the primers) and makes no disclosure as to any other use of the claimed primers in any other type of nucleic acid amplification reaction. Such a limit is evidenced by the assertion "[t]he processes of the present invention offer all the same advantages offered by other amplification reactions, plus additional benefits." Column 12, lines 65-67. The primary benefit disclosed by Wallace is, as discussed above, the inability of the second generation primer extension products to serve as templates for the synthesis of extension products of the primers which were extended to synthesize their templates. It is this process of nucleic acid amplification alone that is disclosed. Nowhere does Wallace disclose any other process or reaction for which to use the disclosed template-deficient oligonucleotide primers.

For the reasons above, Wallace fails to anticipate claims 1, 5, 8-10, 19, 22 and 77. At least for these reasons, the present rejection should be reversed.

Appellants note that the current rejection in the Office Action mailed July 13, 2004 does not cite or rely on Sommer. By discussing Sommer above, Appellants do imply or concede that the present rejection is based on or relies on Sommer. Discussion of Sommer above is only for complete and efficient analysis of the errors in the present rejection.

D. Rejection of claims 1-19, 21, 22 and 77-80 under 35 U.S.C. § 102(e) as anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over Van Ness *et al.*

1. Argument for claims 1-19, 21, 22 and 77-80.

Claims 1-19, 21, 22 and 77-80 are patentable over Van Ness *et al.* as Van Ness *et al.* does not disclose primers that contain template-deficient nucleotides where the number and composition of nucleotides 3' of the template-deficient nucleotide closest to the 3' end is alone sufficient to effectively prime nucleic acid synthesis.

i. The issues

Appellants submit that the present rejection depends on the proper understanding of what the prior art discloses, the proper understanding of what the current claims require, the proper understanding of the law of the novelty and unobviousness requirements as it applies to the claimed method, and a proper application of that law to the claimed method. Appellants note that the rejection fails to achieve any of these goals in the present rejection.

The rejection contends that the claims encompass the use of primers that comprise abasic nucleotides and that Van Ness *et al.* discloses at columns 82-85 primers incorporating abasic and other modified nucleotides. The rejection fails to establish that Van Ness *et al.* disclose primers that contain template-deficient nucleotides where the number and composition of nucleotides 3' of the template-deficient nucleotide closest to the 3' end is alone sufficient to effectively prime nucleic acid synthesis.

ii. The legal standard

Anticipation requires strict identity: each and every element of the claimed invention must be identically set forth in a single prior art reference. *See PIN/NIP, Inc. v. Platte Chemical Co.*, 304 F.3d 1235 (Fed. Cir. 2002).

A determination of obviousness requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991).

iii. The claims on appeal.

The present claims are drawn to a method useful for reducing the formation of artifacts during nucleic acid amplification reactions that involves conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer. Use of the template-deficient oligonucleotides reduces the chance that the oligonucleotide could serve as an effective template in the formation of artifacts. The claims recite specific structures and properties for the template-deficient oligonucleotides. Specifically, independent claims 1, 77, 79 and 80 (from which the remaining claims under rejection depend) provide "...wherein the number and composition of template-capable nucleotides 3'of the template-deficient nucleotide <u>closest</u> to the 3'end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3' end <u>alone</u> to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction" (emphasis added). A careful reading of this claim language shows that the claims identify:

(A) a particular nucleotide in the oligonucleotide (hereinafter "nucleotide (A)", defined as "the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide"),

(B) a particular sub-region of the oligonucleotide (hereinafter "sub-region (B)", defined as the "nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide"--that is, nucleotides 3' of nucleotide (A)), and

(C) a property of this particular sub-region (hereinafter "property (C)", wherein "the number and composition of template-capable nucleotides [in sub-region (B)] is sufficient to allow the template-capable nucleotides [in sub-region (B)] alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction").

Note that property (C) is a property of sub-region (B) alone, not of the template-deficient oligonucleotide as a whole. This distinction is crucial. Further, the claim language also makes clear that property (C) is in reference to the capability of sub-region (B) "in the nucleic acid amplification reaction" (emphasis added). That is, property (C) is not a universal property of the oligonucleotide, exhibited in any and all nucleic acid amplification reactions, but rather is a property that need be present only in the particular nucleic acid amplification reaction being performed. A given oligonucleotide may meet this limitation (i.e., property (C)) in some nucleic acid amplification reactions and not others.

Appendix 3 is a diagram of an example of a template-deficient oligonucleotide as claimed where nucleotide (A) is highlighted in pink and sub-region (B) is highlighted in green.

iv. Van Ness *et al.*

Van Ness *et al.* discloses compositions and methods to increase the specificity of hybridization of nucleic acids and priming of nucleic acids in PCR. Column 10, lines 18-20. The method of Van Ness *et al.* involves the use of primers with an abasic residue, deoxyNebularine residue, or a hybotope with the intention of increasing specificity of binding between the primer and the sequence to be amplified. See Abstract. Van Ness *et al.* fails to disclose the use of template-deficient nucleotides in a primer where nucleotides 3' of the template-deficient nucleotide alone are sufficient to effectively prime nucleic acid synthesis. Van Ness *et al.* provides no suggestion or motivation to use template-deficient nucleotides in a primer where nucleotides 3' of the template-deficient nucleotide alone are sufficient to effectively prime nucleic acid synthesis. Because Van Ness *et al.* fails to disclose each and every feature of the present claims and fails to provide any suggestion or motivation to modify its teachings to arrive at Appellants' claimed method, Van Ness *et al.* fails to anticipate or make obvious the present claims.

v. Van Ness *et al.*'s primers do not have the properties of Appellants' claims

Van Ness *et al.*, at columns 82-85, discloses performing amplification reactions where one or more modified nucleotides are incorporated into a primer. The rejection indicates that in Table 14 and column 84 of Van Ness *et al.* at least one of the primers contains modified nucleotides located at the 5' terminus and within three nucleotides of the 5' terminus. The rejection fails to address use template-deficient nucleotides in a primer where nucleotides 3' of the template-deficient nucleotide alone are sufficient to effectively prime nucleic acid synthesis. The rejection fails to point out how or where Van Ness *et al.* discloses or suggests use template-

deficient nucleotides in a primer where nucleotides 3' of the template-deficient nucleotide alone are sufficient to effectively prime nucleic acid synthesis.

Table 14 of Van Ness *et al.* and the surrounding text show primers that can be placed into three categories:

(A) Primers that Do Not Contain Any Modified Nucleotides

As can be seen from the sequences listed in column 84, lines 47-49, primers H17, H14, and H11 of Van Ness *et al.* do not contain any abasic or modified nucleotides because there are no "dS" or "dN" present in the primer sequences. Further, in Table 14, Van Ness *et al.* discloses that these particular primers only contain mismatches and are without any substitutions. Thus, primers H17, H14, and H11 of Van Ness *et al.* do not contain any template-deficient nucleotides, as required in the present claims.

(B) Primers that Contain Abasic Nucleotides

Primers AB1, AB2 and AB3 of Van Ness *et al.* contain dS (an abasic nucleotide) but amplification does not occur with these primers. Thus, the AB1, AB2 and AB3 have a template-deficient nucleotide but do not effectively amplify nucleic acids in the nucleic acid amplification reaction of Van Ness *et al.* (see column 4 in Table 14). It follows that the nucleotides 3' of the template-deficient nucleotide are not sufficient to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction of Van Ness *et al.* These primers do not meet all of the limitations of claims 1-19, 21, 22 and 77-80.

(C) Primers that Contain deoxyNebularine Nucleotides

Primers DN1, DN2, DN3, DN4, DN5 and DN6 of Van Ness *et al.* contain dN (deoxyNebularine) which is a nucleotide that polymerases can read through. *See* Van Ness *et al.*,

inter alia, at col. 58, lines 33-41. While dN is a "modified" nucleotide, it is not a template-deficient nucleotide. Thus, these primers do not contain any template-deficient nucleotides. Therefore, these primers do not meet all of the limitations of claims 1-19, 21, 22 and 77-80 of the present application. The ability of these primers to prime replication and amplify nucleic acids is irrelevant.

Page 11, line 20 of the present application defines template-deficient nucleotides as "...nucleotides or nucleotide analogs that (when contained in a nucleic acid molecule) cannot serve as a template for nucleic acid synthesis." Column 85, lines 39-41 of Van Ness *et al.* state "[h]owever, the polymerases can read through deoxyNebularine residues present in the oligonucleotide primers." Therefore, by definition, dN is not a template-deficient nucleotide. By way of contrast, column 85, line 35 of Van Ness *et al.* states "[t]hat is, when the polymerase encounters an abasic residue, chain extension is terminated." Chain extension is not terminated with dN. dN is a base analog (see col. 21, lines 23-27) , which is defined in Van Ness *et al.* with the following: "a 'base analog' or 'base analog residue' in an oligonucleotide refers to a molecular fragment that includes a ribofuranose sugar and is substituted at the beta anomeric position with a group similar to that of at least one of the A,C,G,T or U bases, so that a polymerase will read through the base analog..."(Van Ness *et al.*, column 21, lines 15-21 (emphasis added)). Thus, base analogs of Van Ness *et al.* are not template-deficient nucleotides.

Summarizing, the H17, H14 and H11 primers do not contain a template-deficient nucleotide, the AB1, AB2 and AB3 primers do not have the required "effectively prime" property (property (C) of the present claims, discussed above) and the DN1, DN2, DN3, DN4, DN5 and DN6 primers do not contain a template-deficient nucleotide. Thus, none of the primers

in Table 14 of Van Ness *et al.* have all of the features and properties required by the present claims. As Van Ness *et al.* does not meet the limitation of the present claims that the primers contain a template-deficient nucleotide, the position of a different modified nucleotide (i.e. a non-template-deficient nucleotide) in a primer in Van Ness *et al.* does not matter; nor does the fact that these primers result in amplification. Therefore, Van Ness *et al.* does not disclose primers or a method that meet the limitations of the present claims and, as a result, claims 1-19, 21, 22 and 77-80 are not anticipated by Van Ness *et al.* Accordingly, the present rejection should be reversed.

vi. Van Ness *et al.* does not provide any suggestion or motivation to modify its teachings to practice the claimed invention

Van Ness *et al.* provides no suggestion or motivation to use template-deficient nucleotides in a primer where nucleotides 3' of the template-deficient nucleotide alone are sufficient to prime nucleic acid synthesis. Rather, Van Ness *et al.* discloses only the insertion of an abasic nucleotide, deoxynebularine or other modified nucleotide into an oligonucleotide to improve priming specificity since these nucleotides decrease the helical coil transition temperature (HCT) of the oligonucleotide. *See* Van Ness *et al.*, *inter alia*, at Example 6, Table 12. Van Ness *et al.* does not disclose or suggest the placement of template-deficient nucleotides and template-capable nucleotides in any particular arrangement or composition. Van Ness *et al.* does not disclose or suggest placement of template-capable nucleotides 3' to the template-deficient nucleotide in a number and composition so that the 3' template-capable nucleotides alone are capable of effectively priming nucleic acid amplification. Thus, those of ordinary skill in the art reading Van Ness *et al.* would not be directed or guided to make the particular

oligonucleotides used in the claimed method. Therefore, claims 1-19, 21, 22 and 77-80 are not obvious in view of Van Ness *et al.* Accordingly, the present rejection should be reversed.

E. Rejection of claims 1-19, 21, 22 and 77-80 under 35 U.S.C. § 103(a) as being unpatentable over Van Ness *et al.* in view of Gildea *et al.* or Egholm *et al.*

1. Argument for claims 1-19, 21, 22 and 77-80

Claims 1-19, 21, 22 and 77-80 are patentable over Van Ness *et al.* in view of Gildea *et al.* or Egholm *et al.* as none of Van Ness *et al.*, Gildea *et al.* or Egholm *et al.* disclose or suggest primers that contain template-deficient nucleotides where the number and composition of nucleotides 3' of the template-deficient nucleotide closest to the 3' end is alone sufficient to effectively prime nucleic acid synthesis.

i. The issues

Appellants submit that the present rejection depends on the proper understanding of what the prior art discloses, the proper understanding of what the current claims require, the proper understanding of the law of the novelty and unobviousness requirements as it applies to the claimed method, and a proper application of that law to the claimed method. Appellants note that the rejection fails to achieve any of these goals in the present rejection.

The rejection relies on Van Ness *et al.* on the same basis as in the rejection under 35 U.S.C. § 102(e)/103. The rejection fails to establish that Gildea *et al.* or Egholm *et al.* cure or supplement the failings of Van Ness *et al.* The rejection merely contends that it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the procedure of Van Ness *et al.* to include other modified nucleotides, peptide nucleic acids (PNA), as taught by both Gildea *et al.* and Egholm *et al.* The rejection further contends that although Appellants' claims are drawn to specific combinations of modified nucleotides they are

considered to be the result of routine optimization and do not rise to the level of a patentable difference over the prior art since routine optimization is not patentable, even if it results in significant improvements over the prior art.

ii. The legal standard

A determination of obviousness requires consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and (2) whether the prior art would also have revealed that in so making or carrying out, those of ordinary skill would have a reasonable expectation of success. *See In re Dow Chemical Co.*, 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1444 (Fed. Cir. 1991).

A combination of references must expressly or impliedly suggest all of the features of the claimed invention. *In re Gorman*, 933 F.2d 982, 986-987, 18 U.S.P.Q.2d 1885, 1888 (Fed. Cir. 1991). In a proper obviousness rejection based upon a combination of any two or more prior art references, the motivation to combine must be found in the prior art. *W. L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1551, 220 U.S.P.Q. 303, 311-312 (Fed. Cir. 1983). Further, inherency cannot form the basis of an obviousness rejection because obviousness cannot be predicated on what is unknown. *See In re Rijckaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993). It is irrelevant that each aspect of the invention was individually present in the prior art at the time of the invention. Rather, to negate patentability, there must be something in the prior art to suggest the desirability of combining these individual elements as

claimed by the applicant. *Fromson v. Advance Offset Plate, Inc.*, 755 F2d 1549, 1556, 225 U.S.P.Q.2d, 31-32 (Fed. Cir. 1985).

Moreover, the fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness. *In re Baird*, 16 F.3d 380, 382, (Fed. Cir. 1994). Therefore, in order for a genus to render a species obvious, there must be a suggestion in the prior art to modify the genus in order to provide the specifically claimed subgenus or species.

iii. The claims on appeal.

The present claims are drawn to a method useful for reducing the formation of artifacts during nucleic acid amplification reactions that involves conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer. Use of the template-deficient oligonucleotides reduces the chance that the oligonucleotide could serve as an effective template in the formation of artifacts. The claims recite specific structures and properties for the template-deficient oligonucleotides. Specifically, independent claims 1, 77, 79 and 80 (from which the remaining claims under rejection depend) provide "...wherein the number and composition of template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3'end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3'of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction" (emphasis added). A careful reading of this claim language shows that the claims identify:

(A) a particular nucleotide in the oligonucleotide (hereinafter "nucleotide (A)", defined as "the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide"),

(B) a particular sub-region of the oligonucleotide (hereinafter "sub-region (B)", defined as the "nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide"--that is, nucleotides 3' of nucleotide (A)), and

(C) a property of this particular sub-region (hereinafter "property (C)", wherein "the number and composition of template-capable nucleotides [in sub-region (B)] is sufficient to allow the template-capable nucleotides [in sub-region (B)] alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction").

Note that property (C) is a property of sub-region (B) alone, not of the template-deficient oligonucleotide as a whole. This distinction is crucial. Further, the claim language also makes clear that property (C) is in reference to the capability of sub-region (B) "in the nucleic acid amplification reaction" (emphasis added). That is, property (C) is not a universal property of the oligonucleotide, exhibited in any and all nucleic acid amplification reactions, but rather is a property that need be present only in the particular nucleic acid amplification reaction being performed. A given oligonucleotide may meet this limitation (i.e., property (C)) in some nucleic acid amplification reactions and not others.

Submitted with this Appeal Brief is a diagram of an example of a template-deficient oligonucleotide as claimed where nucleotide (A) is highlighted in pink and sub-region (B) is highlighted in green (Appendix 3).

iv. Van Ness *et al.*

Van Ness *et al.* is described above and the description and arguments are incorporated herein.

v. Gildea *et al.*

Gildea *et al.* is applied in the rejection for the general teaching of PNA-DNA chimer synthesis. Gildea *et al.* describes the methods, reagents, structures of the reagents, and conditions employed to synthesize PNA-DNA chimeras. Gildea *et al.* describes the DNA-PNA chimeras essentially as oligomers composed of at least one PNA moiety and at least one DNA moiety. (Column 18, lines 1-3). Gildea *et al.* fails to disclose or suggest the use of template-deficient nucleotides in a primer where nucleotides 3' of the template-deficient nucleotide alone are sufficient to prime nucleic acid synthesis. Gildea *et al.* provides no suggestion or motivation to use template-deficient nucleotides in a primer where nucleotides 3' of the template-deficient nucleotide alone are sufficient to prime nucleic acid synthesis. Because Gildea *et al.* fails to disclose each and every feature of the present claims and fails to provide any suggestion or motivation to modify the teachings of Van Ness *et al.* to arrive at the claimed invention, the combination of Van Ness *et al.* and Gildea *et al.* fails to make obvious claims 1-19, 21, 22 and 77-80.

vi. Egholm *et al.*

Egholm *et al.* is applied in the rejection for its disclosure of performing PCR, RT-PCR using chimeric primers that comprise PNA conjugates. Egholm *et al.* discloses PNA-DNA chimeras. Egholm *et al.* fails to disclose or suggest the use of template-deficient nucleotides in a primer where nucleotides 3' of the template-deficient nucleotide alone are sufficient to prime

nucleic acid synthesis. Egholm *et al.* provides no suggestion or motivation to use template-deficient nucleotides in a primer where nucleotides 3' of the template-deficient nucleotide alone are sufficient to prime nucleic acid synthesis. Because Egholm *et al.* fails to disclose each and every feature of the present claims and fails to provide any suggestion or motivation to modify the teachings of Van Ness *et al.* to arrive at the claimed invention, the combination of Van Ness *et al.* and Egholm *et al.* fails to make obvious claims 1-19, 21, 22 and 77-80.

vii. The primers of Gildea *et al.* and Egholm *et al.* do not have the properties of Appellants' claims

Gildea *et al.* and Egholm *et al.* are simply being applied in the rejection for a generic teaching of PNA-DNA chimeras. The rejection is not citing Gildea *et al.* or Egholm *et al.* for the purpose of satisfying the limitations lacking in Van Ness *et al.*, namely the inability of the nucleotides 3' to the template-deficient nucleotides to alone effectively prime nucleic acid synthesis. Specifically, Van Ness *et al.* in combination with Gildea *et al.* or Egholm *et al.* do not disclose or suggest the placement of template-deficient nucleotides and template-capable nucleotides in any particular arrangement or composition. Van Ness *et al.* in combination with Gildea *et al.* or Egholm *et al* do not disclose or suggest placement of template-capable nucleotides 3' to the template-deficient nucleotide in a number and composition so that the 3' template-capable nucleotides alone are capable of effectively priming nucleic acid amplification. Thus, those of ordinary skill in the art reading Van Ness *et al.* in view of Gildea *et al.* or Egholm *et al.* would not be directed or guided to make the particular oligonucleotides used in the claimed method. Therefore, the present application is patentable over Van Ness *et al.* in view of Gildea *et al.* or Egholm *et al.*

viii. Appellants' claims drawn to specific combinations of modified nucleotides rise to the level of a patentable difference over the prior art.

At best, Van Ness *et al.*, either alone or in combination with Gildea *et al.* or Egholm *et al.*, disclose or suggest oligonucleotides incorporating modified nucleotides generically. There is no disclosure or suggestion to make and use oligonucleotides have the claimed arrangement of template-deficient nucleotides to result in the claimed properties (property (C) in particular). Although the rejection asserts that inventions that can be arrived at through routine optimization from the prior art are not necessarily patentable, this principle is not applicable here at least because the claimed method and oligonucleotides could not be arrived at through routine "optimization" and the rejection has made no showing to this effect.

Again, at best, Van Ness *et al.*, either alone or in combination with Gildea *et al.* or Egholm *et al.*, disclose or suggest oligonucleotides incorporating modified nucleotides generically. Even if this were the case, it would not be enough to make obvious the primers recited in the claims because a generic disclosure encompassing numerous compounds does not render obvious a claim to a subgenus of compounds encompassed by the generic disclosure if that disclosure fails to suggest or point out why, among all the other compounds, one would seek the subgeneric compounds being claimed. *See In re Baird*, 16 F.3d 380, 382, (Fed. Cir. 1994). Van Ness *et al.*, Gildea *et al.* and Egholm *et al.* fail to provide any description or suggestion as to the placement of template-capable nucleotides 3' to the template-deficient nucleotide in a number and composition so that the 3' template-capable nucleotides alone are capable of priming nucleic acid amplification. Therefore, Van Ness *et al.* in combination with Gildea *et al.* and Egholm *et al.* fail to provide any guidance for arriving at what is claimed and fail to provide any

basis or direction for any "optimization, routine or otherwise, that could result in what is claimed. In this regard, the reference in the rejection to routine optimization is misplaced. Therefore, for at least these reasons, this rejection is in error and should be reversed.

VII. SUMMARY AND CONCLUSION

Appellants have established that the claimed method is both definite as well as proper and statutory subject matter. In particular, Appellants have provided clear evidence that one skilled in the art, having the Appellants' disclosure and claims before him, would be possessed of a reasonable degree of certainty as to the subject matter encompassed within the claim. Appellants have also shown that the evidence and argument presented in the rejection regarding the alleged indefiniteness of the claims is based on an improper legal standard.

Appellants have established that the claimed method is not anticipated by Wallace. In particular, Appellants have established that Wallace does not disclose or suggest placement of template-capable nucleotides 3' to the template-deficient nucleotide in a number and composition so that the 3' template-capable nucleotides alone are capable of effectively priming nucleic acid amplification as required by the claims.

Appellants have also established the claimed method is not anticipated nor made obvious by Van Ness *et al.*. In particular, Appellants have established that Van Ness *et al.* does not disclose or suggest disclose or suggest placement of template-capable nucleotides 3' to the template-deficient nucleotide in a number and composition so that the 3' template-capable nucleotides alone are capable of effectively priming nucleic acid amplification as required by the claims.

Appellants have also established the claimed method is not obvious over Van Ness *et al.* in combination with Gildea *et al.* or Egholm *et al.*. In particular, Appellants have established Van Ness *et al.* in combination with Gildea *et al.* or Egholm *et al.* do not disclose or suggest placement of template-capable nucleotides 3' to the template-deficient nucleotide in a number and composition so that the 3' template-capable nucleotides alone are capable of effectively priming nucleic acid amplification as required by the claims.

For the foregoing reasons, the rejections of claims 1-19, 21, 22 and 77-80 should be reversed.

Respectfully submitted,

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Robert A. Hodges — Date 9/6/2005

VIII. Claims Appendix (Appendix 1)

1. A method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising

conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer,

wherein the template-deficient oligonucleotide comprises one or more template-deficient nucleotides,

wherein the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction.

2. The method of claim 1 wherein the one or more template-deficient nucleotides are at the 5' end of the template-deficient oligonucleotide.

3. The method of claim 1 wherein the template-deficient oligonucleotide comprises two or more template-deficient nucleotides, wherein at least two of the two or more template-deficient nucleotides are adjacent.

4. The method of claim 3 wherein the two or more adjacent template-deficient nucleotides are within three nucleotides of the 5' end of the template-deficient oligonucleotide.

5. The method of claim 1 wherein the template-deficient nucleotides are selected from the group consisting of modified nucleotides, derivatized nucleotides, ribonucleotides, and nucleotide analogs.

6. The method of claim 1 wherein the template-deficient oligonucleotide comprises two or more template-deficient nucleotides, wherein at least two of the two or more template-deficient nucleotides are different.

7. The method of claim 1 wherein the template-deficient oligonucleotide comprises two or more template-deficient nucleotides, wherein at least two of the two or more template-deficient nucleotides are template-deficient for different reasons.

8. The method of claim 5 wherein the template-deficient nucleotides are modified nucleotides.

9. The method of claim 5 wherein the modified nucleotides are abasic nucleotides.

10. The method of claim 5 wherein the template-deficient nucleotides are selected from the group consisting of abasic nucleotides, nucleotides with an inverted base, fluoro substituted nucleotides, alkyl substituted nucleotides, nucleotides with phenyl substituted ethers, nucleotides with substituted thioethers, nucleotides with phosphate esters, -nucleotides, 2',3'-dideoxy nucleotides, ribonucleotides, nucleotides derivatized with biotin, nucleotides derivatized with amine, nucleotides derivatized with Hex, nucleotides derivatized with Tet, nucleotides derivatized with Fam, nucleotides derivatized with fluorescein, nucleotides derivatized with rhodamine, nucleotides derivatized with alkaline phosphatase, nucleotides derivatized with horseradish peroxidase, nucleotides derivatized with spacers, nucleotides derivatized with cholesteryl, nucleotides derivatized with DNP-TEG, nucleotides derivatized with psoralen cross-linkers, nucleotides derivatized with intercalating agents, and nucleotides derivatized with PNA conjugates.

11. The method of claim 1 wherein the nucleic acid amplification reaction does not involve cycle sequencing.

12. The method of claim 11 wherein the nucleic acid amplification reaction does not require linear amplification via thermal cycling.

13. The method of claim 12 wherein the nucleic acid amplification reaction does not involve linear amplification via thermal cycling.

14. The method of claim 1 wherein the nucleic acid amplification reaction involves exponential amplification via thermal cycling.

15. The method of claim 14 wherein the nucleic acid amplification reaction requires exponential amplification via thermal cycling.

16. The method of 14 wherein the nucleic acid amplification reaction involves the polymerase chain reaction.

17. The method of claim 1 wherein the nucleic acid amplification does not involve thermal cycling.

18. The method of 17 wherein the nucleic acid amplification is rolling circle amplification.

19. The method of claim 1 wherein the nucleic acid amplification reaction is selected from the group consisting of exponential rolling circle amplification (ERCA), rolling circle amplification (RCA), multiple displacement amplification (MDA), strand displacement amplification (SDA), nucleic acid sequence based amplification (NASBA), transcription-mediated amplification (TMA), polymerase chain reaction (PCR), self-sustained sequence replication (3SR), amplification with Q replicase, and cycle sequencing.

21. The method of claim 1 wherein all of the primers used in the nucleic acid amplification reaction are template-deficient.

22. The method of claim 1 wherein all of the oligonucleotides used in the nucleic acid amplification reaction are template-deficient.

77. A method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising

conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer,

wherein the template-deficient oligonucleotide comprises one or more template-deficient nucleotides, wherein the one or more adjacent template-deficient nucleotides are within three nucleotides of the 5' end of the template-deficient oligonucleotide,

wherein the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction.

78. The method of claim 77, wherein the modified nucleotides are abasic nucleotides.

79. A method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising

conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer,

wherein the template-deficient oligonucleotide comprises one or more template-deficient nucleotides, wherein the modified nucleotides are abasic nucleotides,

wherein the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction.

80. A method of reducing formation of artifacts in a nucleic acid amplification reaction, the method comprising

conducting a nucleic acid amplification reaction using a template-deficient oligonucleotide as a primer,

wherein the template-deficient oligonucleotide comprises one or more template-deficient nucleotides, wherein the one or more adjacent template-deficient nucleotides are within three nucleotides of the 5' end of the template-deficient oligonucleotide, wherein the modified nucleotides are abasic nucleotides,

wherein the number and composition of template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end of the template-deficient oligonucleotide is sufficient to allow the template-capable nucleotides 3' of the template-deficient nucleotide closest to the 3' end alone to effectively prime nucleic acid synthesis in the nucleic acid amplification reaction.

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Appendix 2

FIG. 1

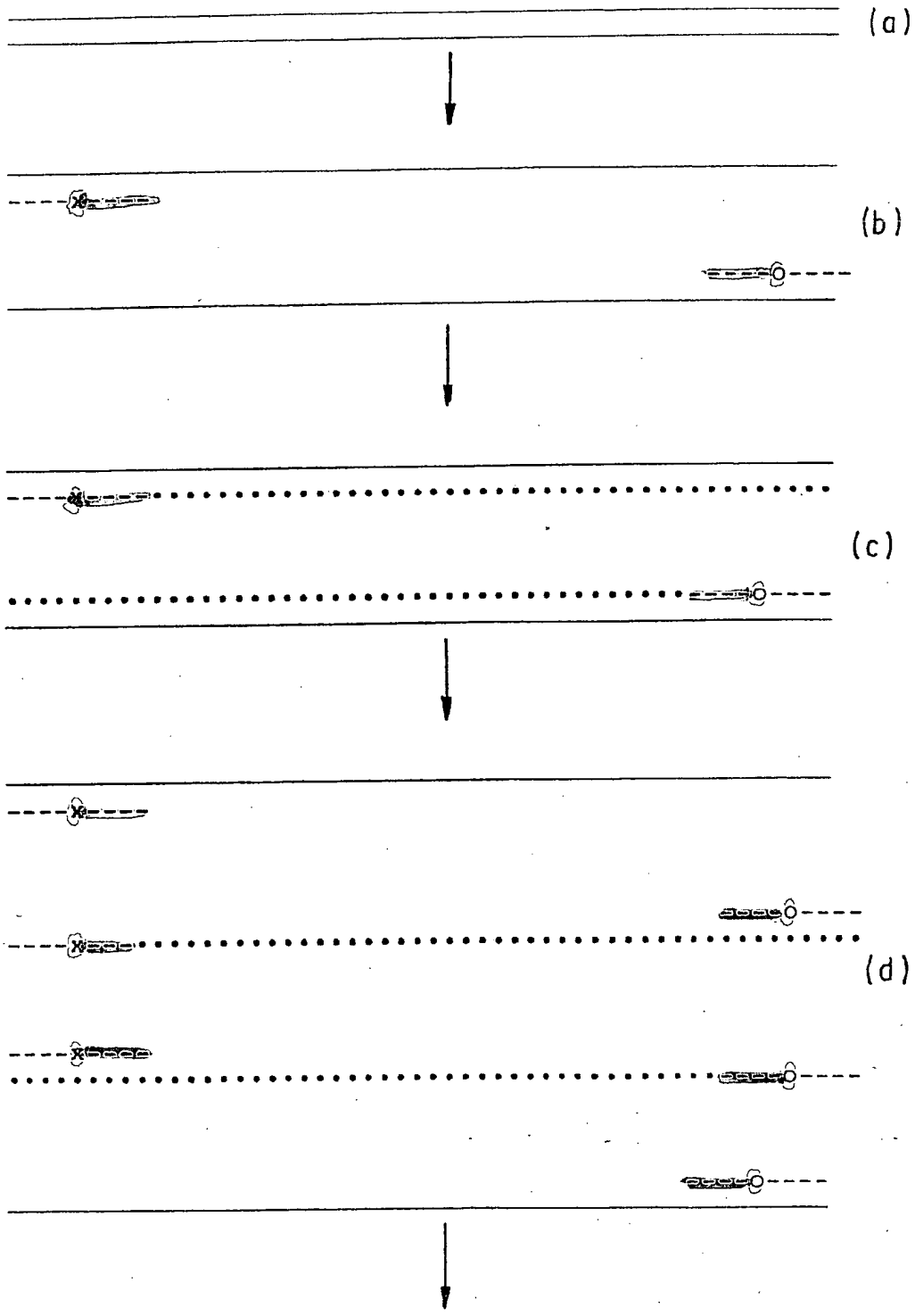


FIG.2

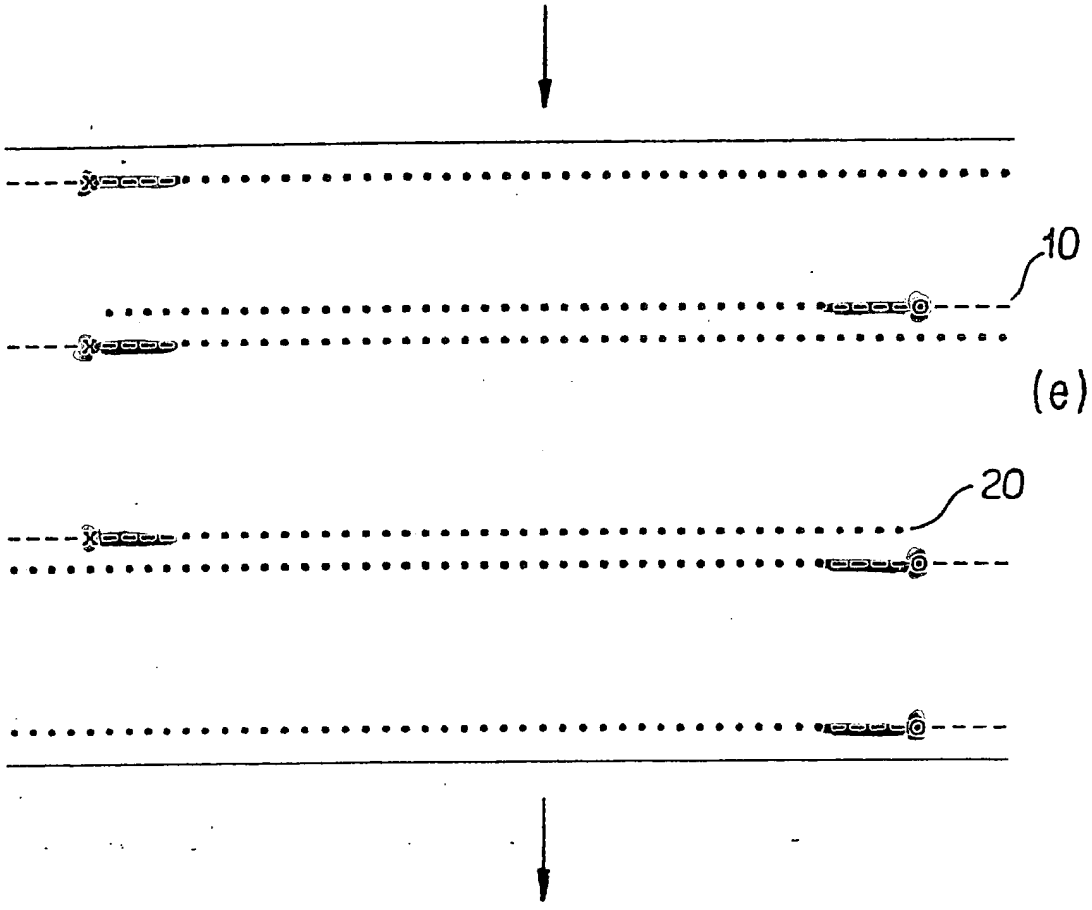


FIG.3

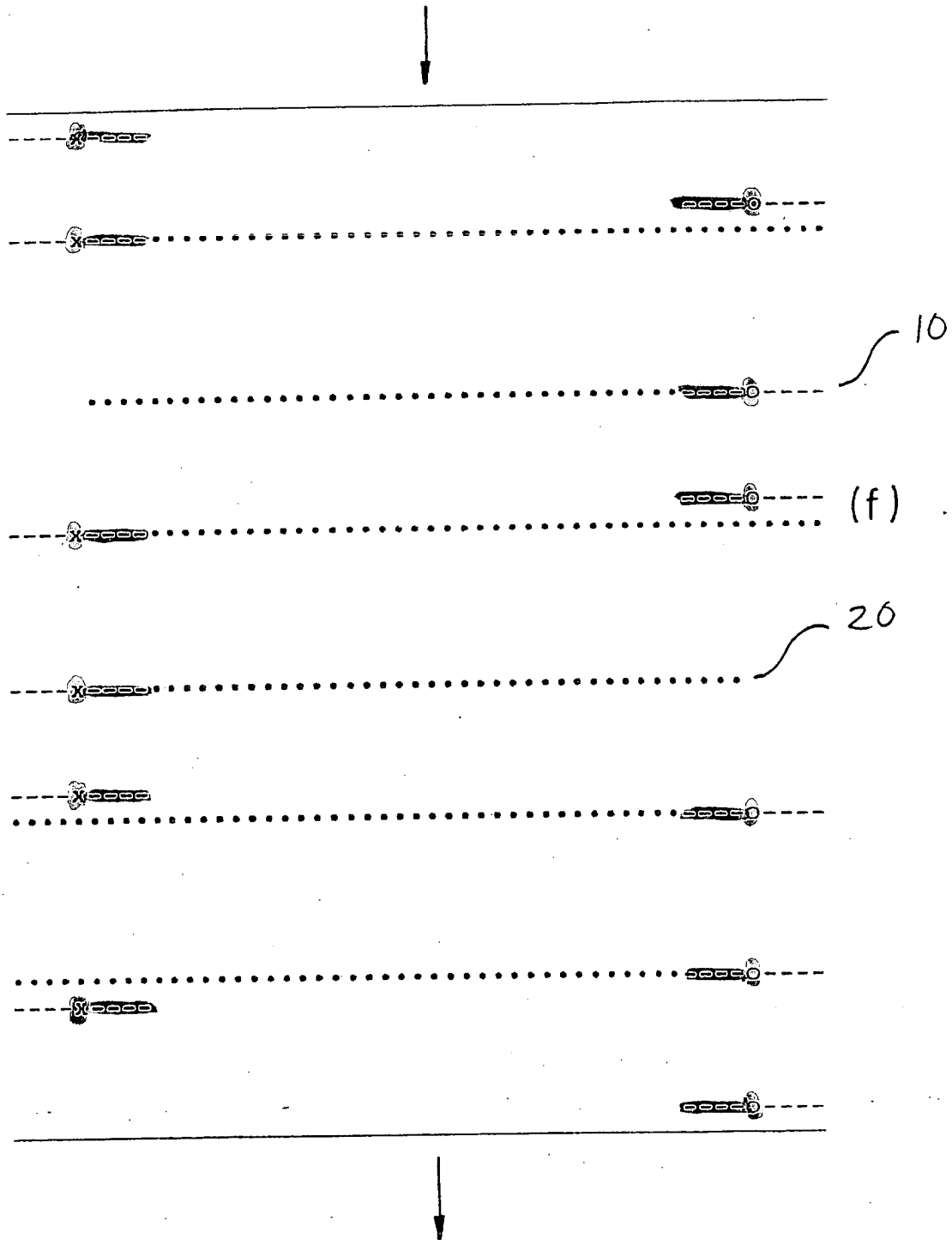
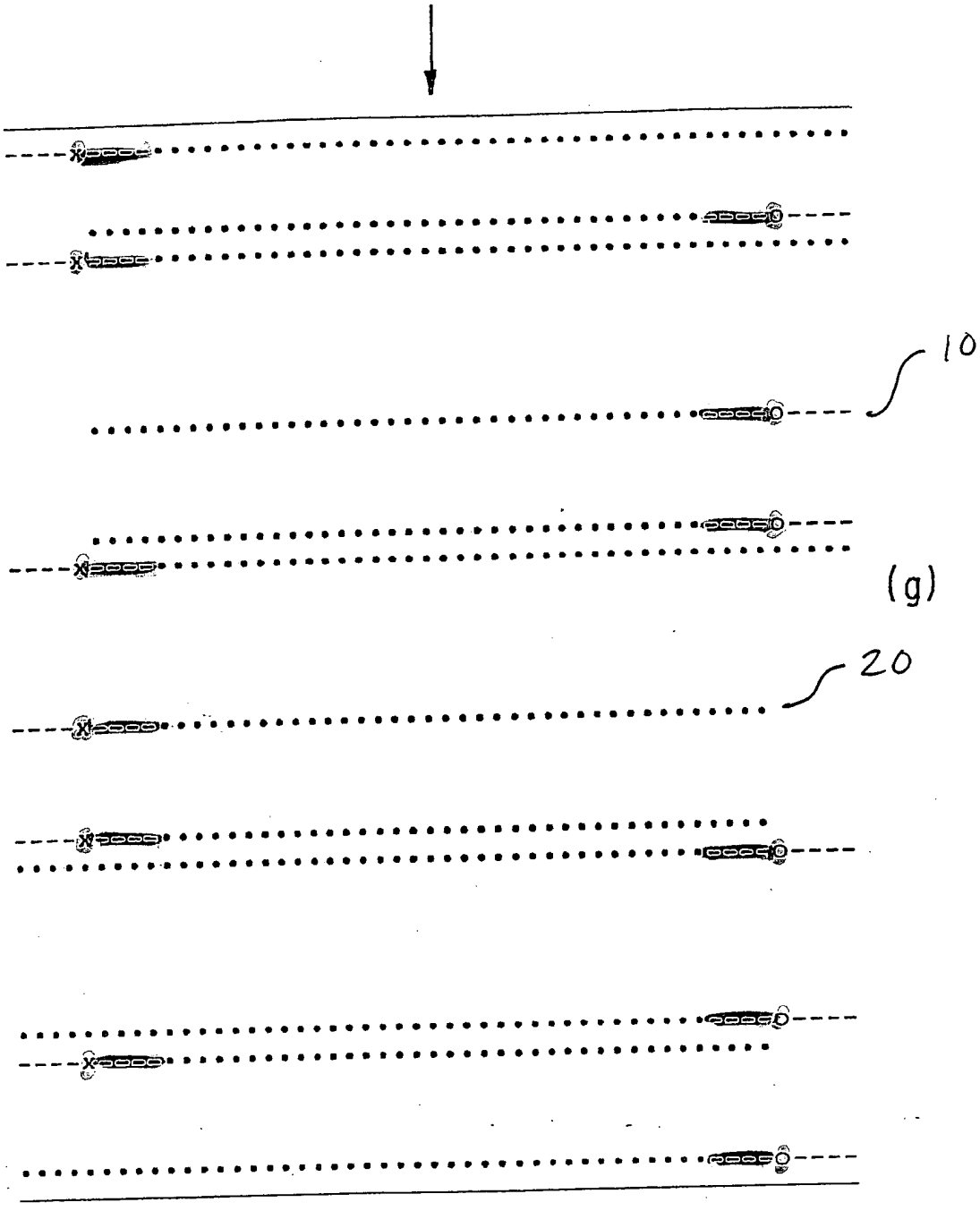


FIG.4



Appendix 3